milieu of GvHD includes IL-6, IL-12, and IL-23, favoring Th1/Th17 differentiation over that of regulatory T cells (Treg). We show that blockade of IL-6-receptor-alpha *in vitro* with tocilizumab (humanized Mab, 5 ug/ml) fails to alter alloreactive T cell proliferation (P = NS, n = 4), Treg expansion (8.87 v 9.90%, P = NS, n = 4), or Th1/Th17 differentiation (19 v 19.6%, 1.32 v 1.53%, P = NS, n = 3). Janus kinase 2 (JAK2) relays downstream signaling by IL-6, IL-12, and IL-23, through the phosphorylation of signal transducer and activator of transcription 3 (STAT3). We demonstrate that TG101348, a very specific, small molecule inhibitor of JAK2, when present during initial and secondary encounters between human T cells and fully HLA-disparate, allogeneic monocyte-derived dendritic cells (moDCs), induces durable and specific T cell tolerance on reexposure to the priming alloantigens. TG101348 ablates the IL-6/JAK2/pSTAT3 pathway in T cells (24 v 0%, P<0.05, n = 5) without off-target effects on IL-2 or IL-15/JAK3/pSTAT5-dependent signaling, which would interfere with Treg development and important effector T-cell responses. JAK2 inhibition enhances the ratio of $CD4^+$ Tregs to $CD8^+CD25^+$ effector T cells in favor of Tregs (Treg:Effector 1:2 vs 1:1, P<0.05, n = 5). JAK2 inhibition also reduces IL-6 (255 vs 157 pg/ml, P<0.05, n = 5) and TNF-alpha (50 vs 15 pg/ml, P<0.05, n = 4) production in allogeneic MLRs, impairing the activation of central and effector memory T cells, as well as the expansion of responder Th1 (24 vs 14%, P<0.05, n = 4) and Th17 (2 vs 1%, P<0.05, n = 4). T cells primed by allogeneic moDCs have a profound inability to respond upon reexposure to fresh allogeneic moDCs from the original stimulator, whether the JAK2 inhibitor were present in either the primary or the secondary MLR (P<0.05, n = 4). This indicates that TG101348 can prevent initial sensitization, as well as recall responses by already sensitized T cells, to alloantigen. Responses to stimulation *de novo* by influenza matrix peptide (fluMP), a pathogenic nominal antigen, remain intact (P = NS, n = 4). JAK2 inhibition, but not IL-6 blockade alone, therefore induces durable tolerance in HLA-disparate pairings, without broader immune impairment. These findings provide a strong rationale for exploring this strategy in both GvHD prophylaxis and treatment.

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HLA MATCHED RELATED BONE MARROW TRANSPLANTATION IN 85 PATIENTS WITH FANCONI ANEMIA: THE BRAZILIAN EXPERIENCE USING CYCLOPHOSPHAMIDE 60MG/KG

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Fanconi anemia(FA) is a rare disease characterized by progressive bone marrow failure, congenital anomalies and striking predisposition to cancer. BMT is indicated for pts who develop pancytopenia, myelodysplasia or acute leukemia. During the past 30 years we have progressively decreased the dose of Cyclophosphamide(CY) in the preparatory regimen which resulted in a significant increase in survival.

Objective: Analyze the outcome of 85 pts with FA submitted to an HLA matched related BMT in 6 Brazilian centers using CY 60mg/kg as the preparatory regimen.

Patient and Methods: Period: 07/1999-05/2011. Gender: 40F/45M. Age 3-34 years (M: 9). Type of donor: Siblings:74pts; other related: 11pts. Eighty-two pts had severe pancytopenia while 3 had overt myelodysplastic syndrome(MDS). All received the same preparatory regimen with CY60mg/kg and GVHD prophylaxis with cyclosporin and methotrexate.

Results: 72 pts are alive between 5 months and 12 ys after BMT (M:5ys) with an overall survival (OS) of 85% in 5 ys. Pts transplanted under the age of 10(48pts) had an OS of 95,6% in 5ys. Two pts died before D+28 and were not evaluable for engraftment. Rejection occurred in 6 pts: 2 had primary graft failure and both are alive and well after a 2nd BMT(same donor). Late graft failure occurred in 4 pts at a median of 244 days after BMT(range: 152- 365 days). Three pts underwent a 2nd BMT (same donor) and 2 are alive and well 8 and 10 ys after transplant. All pts with overt MDS relapsed and died of progressive disease despite a 2nd BMT. Mucositis grade II-III occurred in 80%. Seventeen of 81 evaluable pts developed Acute-GVHD (grade III: 4pts, grade IV: 3pts) while 23/78 evaluable pts had chronic-GVHD (extensive: 12 pts). In multivariate analysis, only acute and chronic GVHD were associated with a lower OS. Four pts developed carcinoma of the tongue between 2 and 5 years after BMT, two are alive and one has active disease. All had extensive C-GVHD involving the oral mucosa. Thirteen pts died between 12 and 2034 days after BMT (M: 256 days). The major causes of death were related to GVHD/infections and rejection. TRM at 100 days was 6% and at 1 year was 10%.

Conclusions: This regimen is well tolerated and associated with an excellent survival especially in children younger than 10 years. Acute and chronic GVHD had an impact in overall survival and strategies are being developed to reduce this complication.

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IMPACT OF CHRONIC GVHD ON LATE RELAPSE, TREATMENT RELATED MORTALITY AND SURVIVAL AFTER ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION FOR HEMATOLOGICAL MALIGNANCIES

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Disease relapse remains a major obstacle to successful allogeneic hematopoietic cell transplantation (HCT). The development of chronic graft-versus-host disease (cGVHD) has been associated with fewer relapses. However, the peak incidences of early relapse and cGVHD commonly overlap after HCT and variations in treatment make it difficult to evaluate the relative impact of cGVHD on HCT outcomes. In this study, we investigated the association of cGVHD and the incidence of late relapse (>12 months) after HCT. The study included patients who were alive and disease free at one year after HCT. We also assessed the impact of cGVHD on treatment related mortality (TRM), disease free survival (DFS) and overall survival (OS) for 1 year disease-free survivors. The study included 7489 recipients of HCT from HLA-identical siblings or URDs conditioned with high intensity regimens for acute myeloid leukemia (AML), acute lymphoid leukemia (ALL), chronic myeloid leukemia (CML), or myelodysplastic syndrome (MDS) between 1995 and 2004 and reported to the Center for International Blood and Marrow Transplant Research. Forty-seven percent of the study population was diagnosed with cGVHD within 12 months of HCT. The protective effect of cGVHD on late relapse was limited to patients diagnosed with CML (RR: 0.47, 95% CI: 0.37-0.59, P<0.0001). Other factors significantly associated with a lower risk of relapse were early diagnosis of acute GVHD (within 29 days of HCT), grafts from well-matched or partially-matched URD, and GVHD prophylaxis other than T-cell depletion. cGVHD was significantly associated with a higher risk of TRM (RR: 2.43, 95% CI: 2.09-2.82, P<0.0001) and inferior OS (RR: 1.56, 95% CI: 1.41-1.73, P< 0.0001). A separate analysis was performed for CML patients to evaluate the impact of cGVHD specific variables